

THE CHEMICAL INVESTIGATION OF SOME POISON- OUS PLANTS IN THE N.O. SOLANACEÆ.

PART IV.—THE CHEMISTRY OF THE DUBOISIAS.

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The genus of Australian plants known as *Duboisia* consists of three or possibly four species. Two of these are well known—*D. myoporoides* and *D. Hopwoodii*, and have formed the subject of numerous investigations by chemists, pharmacologists, and physicians during forty years. In regard to their active principles, they are perhaps the most interesting of all our native flora, and have received greater attention than any others. The third—*D. Leichhardtii*—is a Queensland species, and nothing is known of its chemical composition or active constituents. *D. Campbelli* has been recorded as probably a new species, but apparently it has never been botanically described. It was found in Western Australia ten years ago, and since the first record appeared (Journ. W. Aust. Nat. Hist. Soc., 1906) nothing further concerning it has been made known.

DUBOISIA MYOPOROIDES R.Br.

i. This evergreen tree is native to Eastern Australia and the islands to the north. Its range extends from the Shoalhaven River in the south to Cape York, and is continued into New Guinea, the Philippine Islands, and New Caledonia. It was described in 1810 by R. Brown(17), who named the genus after the French botanist Dubois. Brown placed it in the family Solanaceæ; Bentham transferred it to Scrophulariaceæ; and when

its poisonous properties had been discovered, von Mueller replaced it among the familiar poison-plants of the Solanaceæ.

ii. It was well known to the aborigines as a poison-plant, and we have the first intimation of its powerful properties from Woolls(18), about 1860. "The aborigines make holes in the trunk and put some fluid in them, which when drunk on the following morning produces stupor. . . . Branches are thrown into pools for the purpose of intoxicating the eels and bringing them to the surface. . . . Branches hung up in a close room have had the effect of producing giddiness and vomiting."

iii. About this same time, another and somewhat similar plant had been brought back from the interior of Australia by the Burke and Wills Expedition, and this plant was described by von Mueller(1a) as *Anthocercis Hopwoodii* (Hopwood being the chief subscriber to this expedition). Bancroft, in 1872, obtained from travellers in the interior, specimens of a plant greatly prized by the aborigines, and which they called "pituri"; and in 1876 von Mueller and Bailey identified pituri with *Anthocercis Hopwoodii*, by the microscopic structure of the leaves. Previous to this, Bentham had doubted the position given to this plant by von Mueller, and in 1876 the latter, after receiving fruiting-specimens from the Giles Expedition(1c), transferred it, at Dr. Bancroft's suggestion, to the genus *Duboisia*.

Bancroft, having learned that pituri was used by the aborigines as a narcotic, made extracts and tried the effects on animals(19). His interesting results at once suggested the examination of the other species of *Duboisia*, which was apparently never suspected of having valuable properties. Von Mueller wrote, in 1877, that *D. myoporoides* probably shares the same properties as *D. Hopwoodii*, since both have the same burning acrid taste; and that the properties of both *Duboisias* will prove similar to those of stramonium.

iv. At von Mueller's suggestion, Bancroft then made watery extracts of the leaves of *D. myoporoides*, and after injecting small amounts into domestic animals, he observed that the "pupil of the eye was always widely expanded, that the animals

walked as if blind, and if let alone fell asleep"—properties quite different from those he had observed in pituri. He then tried the effect of dropping the extract into the eye of animals and also into the human eye, and again after a few minutes wide dilation was observed. Bancroft then sent some of his aqueous extracts to ophthalmic practitioners in Brisbane, Ipswich, and Sydney hospitals. By them, his observations were confirmed, and the midriatic properties were carefully studied on the human eye. The reports of their work are contained in Bancroft's paper on "Pituri and Duboisia"(3). Bancroft used the Duboisia regularly instead of atropia in his ophthalmic practice, and also used it in cases of asthma. The main effects observed were midriasis, confusion of intellect, thirst, and loss of taste.

v. It was in 1877 that Staiger, then Queensland Government Analyst, first prepared the active principle of *D. myoporoides*, from Bancroft's material(6). He found it to be "a yellow oily-looking substance, which refused to crystallise either alone or with acids, and not volatile at 212°F."

vi. At the end of 1878, Bancroft visited England, and took with him specimens of the plant and a few pounds of the extract, which he distributed among various experts for further investigation.

Ringer and Tweedie(20) made a detailed study of the properties of the extract, and of the effects on the eye. Tweedie first brought the drug before the medical world in England. Holmes(21) gave a general account of all the previous work before the Pharmaceutical Society, and at the discussion of the paper, Gerrard stated that "the extracts used were bad pharmaceutical preparations, having the appearance of resinous watery extracts, very acid, therefore likely to be irritating." Gerrard(22) afterwards prepared the active principle from the extracts supplied to him through Holmes. His method was solution in alcohol, evaporation, and removal of the alkaloid with chloroform, solution in acid water, and precipitation by ammonia. The precipitated alkaloid quickly formed heavy oily drops which were left as a yellow viscid mass. Its chemical reactions were then compared with those of atropine, and found to be different.

Drs. Ringer and Murrell(23), working with Gerrard's alkaloid, made careful experiments on its physiological action. They observed dilatation of the eye, the action on the skin in arresting perspiration, headache and drowsiness, the antagonism to muscarine, and the production of tetanus in frogs. The authors concluded, from both physiological and chemical evidence, that the alkaloid was not atropine.

Paul(24), in 1878, further examined the alkaloid prepared by Gerrard, and confirmed the latter's results.

vii. Petit, of Paris(11), in 1879, identified the alkaloid of pituri as nicotine, and also prepared the alkaloid of *D. myoporoides* from an aqueous extract of the leaves. In a letter to Holmes, which is included in Paul's paper, Petit pointed out the differences from atropine.

In the Lancet for 1879, eight cases of poisoning from the use of duboisia were described by Davidson(25); the symptoms were giddiness and delirium. Tweedie ascribed the cause to impurities, but he afterwards found that his own pure solutions, which he had used with Dr. Ringer, produced the same toxic symptoms.

Dr. Norris(26) found the therapeutic action similar to atropine, but more energetic. Ringer(27) also described the action as far more powerful than atropine.

viii. Baron von Mueller and Rummel(28), in January, 1879, described their preparation and the properties of "Duboisine," the alkaloid of *D. myoporoides*. They state that the alkaloid was prepared like nicotine from the leaves and twigs, that it was a *volatile*, yellow, oily liquid, lighter than water, having a strong odour of tobacco and cantharides, and probably identical with "piturine" from *D. Hopwoodii*. The reaction was strongly alkaline.

In another paper, dated September, 1879, the above account is confirmed(29). Von Mueller says: "Piturine is in some respects allied to nicotine, but more closely akin to duboisine (of *D. myoporoides*), the latter being lighter in colour, of bitter, not acrid, taste, and of fainter odour."

In Czapek's text-book—*Biochemie der Pflanzen*, p.311—the statement occurs that "*Duboisia Hopwoodii* contains 1.1% of an alkaloid, earlier known as piturine, which is identical with hyoscyamine." And again, in Wehmer's text-book—*Die Pflanzenstoffe*, p.695, the same erroneous statement is found. There is no doubt that the name "duboisine" has been used for the alkaloid of both plants.

ix. About this time, Ladenburg was investigating the constitution of the atropine group of alkaloids, and their relation to one another. After reading the account of Gerrard's work, he concluded that a more accurate chemical investigation was necessary to decide the true nature of duboisine. Since only two strongly midriatic alkaloids were known to occur naturally—atropine and hyoscyamine,—Ladenburg set out to determine whether duboisine was identical with one of these, or a new tropeine alkaloid. This was all the more interesting as "datu-rine," the alkaloid in *Datura stramonium*, had already been shown to be atropine, by Planta, but was subsequently proved by Ladenburg (34) himself to be identical with its isomer hyoscyamine. Ladenburg received from Merck, in 1880, a few grams of duboisia sulphate in the form of a resinous residue. By carefully purifying the gold salt, he finally obtained the very characteristic crystals of gold hyoscyamine, m.p. 159°C. (33).

Shortly after this, in 1880, Gerrard (36) announced to the Pharmaceutical Society of London that he had succeeded in preparing crystallised duboisine. This he obtained in two different forms by a certain solvent (which he does not mention), and he was unable to say whether these were of the same or different constitution.

In 1882, Gibson (37) studied the action of *Duboisia* on the circulation, and his results showed the typical action of the atropine group.

Professor Harnack (39), the pharmacologist, subsequently challenged Ladenburg's statement that duboisine and hyoscyamine are identical, and affirmed that the former was much stronger. Ladenburg (40) was accordingly induced to return to the subject, and, in 1887, having obtained a few grams of the commercial

duboisine from Merck, he prepared the gold salt of hyosine, m.p. 197-8°C. The mother-liquor yielded no other alkaloid, so that this time no hyoscyamine was present. The author attributed the different results to variations in the method of manufacture.

Shortly afterwards (1890), Messrs. Schering and Co. (41) treated a quantity of the leaves of *D. myoporoides* for alkaloid, and obtained the sulphate of a base showing identical properties with hyoscyamine sulphate, while, from the mother-liquor, hyoscine was obtained.

According to Schmidt (42) and Merck, Ladenburg's hyoscine, which he discovered in the henbane in 1880 and in Duboisia in 1887, was identical with scopolamine, and Schmidt identified his scopolamine in small quantities in the leaves of *D. myoporoides* in 1888. The next account is that of Bender, who obtained samples of the leaves from two different sources. He obtained scopolamine in one, and hyoscyamine in the other. Bender brought his samples to Schmidt, who immediately confirmed these results. Schmidt (42) also obtained, at this time, large quantities of leaves from Schuchart, of Görlitz. He prepared the gold salt, and could find no hyoscyamine or atropine, but only the brilliant, serrated needles of the salt of inactive scopolamine (m.p. 208°C.). Schmidt here states that the previous assumption of Ladenburg is incorrect, but the variation is due to the fact that duboisia leaves of commerce sometimes contain one and sometimes the other base.

x. In 1892, E. Merck (45) discovered in *D. myoporoides* a new midriatic alkaloid which he named pseudo-hyoscyamine. He identified the bases scopolamine and hyoscyamine, and showed that the new base was different from these (m.p. of gold salt, 176°C.). He also stated that the analytical data suggested the probability that the gold salt contained an admixture of still another base with lower molecular weight.

In the large quantities of uncrystallisable aurichloride residues, Merck recognised considerable amounts of amorphous bases which contained none of the alkaloids mentioned.

xi. In 1895, Dr. Lauterer (47), of Brisbane, gave an account of some tests on the alkaloids which he extracted from this

plant. He found, by Gerrard's colour-test with mercuric chloride solution, that hyoscyamine alone was present in old leaves and twigs, but that the fresh young leaves contained mostly scopolamine.

From this period, the chemistry of *Duboisia* was neglected for seventeen years, till, in 1912, the Wellcome Research laboratories received a large supply of the plant from the Philippine Islands. Carr and Reynolds(50) obtained from this material 1.1% of hyoscyamine and 0.15% of pseudo-hyoscyamine. The latter alkaloid was found by them to possess the constitution of nor-hyoscyamine, but they detected no scopolamine in this material.

DUBOISIA HOPWOODII F.v.M.

xii. The poisonous principle of the "pituri" plant was studied by medical specialists in Great Britain in 1878, and the chemist Gerrard(7) found an alkaloid present which he named "piturine." In 1879, Petit, of Paris(11), showed that the alkaloid was nicotine. In 1880, Professor Liversidge revised the analytical work, and obtained a formula for the alkaloid, of lower molecular weight than nicotine: the difference lay in the determination of the nitrogen. It stood thus doubtfully as a new alkaloid under the name of "piturine" for thirty years. Petit's results were recently confirmed by the late Dr. Rothera, of Melbourne(15), and the base has been shown to be identical with nicotine in its chemical, physical, and pharmacological properties. Hartwich(14) in 1910, and Senft(16) in 1911, wrote good descriptive accounts of the plant, including the histology of the leaves and stems, and showing a number of sections. Hartwich compares the histology of the two species. In both accounts, the chemical data show all the positive reactions of nicotine, although the alkaloid is referred to as "piturin." Senft obtained his pituri and information from two Austrian scientists, Domin and Danes, who visited Australia in 1910. All these were unacquainted with Rothera's results. This plant is a shrub or small tree growing to an average height of about eight feet. It is found only in the interior of the continent; it crosses the border on the east

into New South Wales and Queensland; and, on the other side, it extends into Western Australia almost to the centre of that State (J. H. Maiden).

CRITICAL REVIEW OF THE CHEMISTRY OF THE DUBOISIAS.

xiii. The earlier investigators of the Duboisias were apparently impressed by the very great similarity in the general appearance and morphology of the two species. This is evident in their methods of working as well as in their manner of writing; and one sees in their chemical investigations that they suspected the poisonous principles, too, would be found similar in nature. Accordingly, we find it stated that Staiger first isolated the two volatile alkaloids "piturine and duboisine." An alkaloid was prepared from *D. myoporoides* by von Mueller and Rummel, in the same way as nicotine from tobacco. It was a volatile, oily, liquid alkaloid, having a strong odour of tobacco, and was considered as probably identical with piturine. Branches of *D. myoporoides* hung up in a close room produced giddiness and vomiting. Von Mueller and Rummel described the alkaloid obtained by them from *Duboisia Hopwoodii* (pituri) under the name "Duboisine" (10).

On the other hand, the more recent investigations show that *D. myoporoides* contains only the non-volatile alkaloids of the atropine group.

One can only conclude from this conflicting evidence regarding the nature of the active principles, that the earlier workers obtained in their researches, certain incomplete results which were wrongly interpreted by them, and that some authors confused the two plants, or were unaware of the existence of two Duboisias.

A few experiments are now described, which were suggested by the above statements, chiefly to decide the question as to whether in *D. myoporoides* there is present any volatile active principle.

EXPERIMENTAL.

xiv. *Method*:—Fresh plants of *D. myoporoides* were ("treated in the same way as for the extraction of nicotine from tobacco")

crushed, and placed in a distillation flask fitted with a spray-trap. Lime or soda in excess was added, and the whole mass distilled in a current of steam for five or six hours. The ammoniacal distillate was neutralised with acid and concentrated on the water-bath to small volume. The remaining fluid was shaken out, first with ether in presence of acid, then with chloroform after making alkaline. The chloroform was carefully washed and dried, and distilled to remove the solvent. The residue was then weighed and titrated.

Material was obtained from the Sydney Botanic Gardens, the National Park, the North Coast district of New South Wales, and from Queensland. The plants were collected at different seasons throughout the year.

Results :—The ether extracts contained a volatile essential oil of most disagreeable odour.

From eleven separate distillations of the above material, there was obtained, on evaporating the chloroform extract, a small residue, which contained alkaloid in every case. The amounts roughly correspond to 1-2 mgs. per hour of distillation.

xv. *Composition of the volatilised substance* :—

(a) Titration, with centinormal solutions and iodeosin indicator, showed that each of these residues left on evaporation of the chloroform, consisted of about half its weight of an alkaloid.

(b) The residues were yellowish-brown syrups. They were dissolved in a little acidulated water, and the following tests applied. The solutions possessed an intensely bitter taste, and alkaline reaction to litmus.

(c) The general reagents for alkaloids, viz., Wagner's, Mayer's, and Sonnenschein's solutions, picric, tannic, and phosphotungstic acids all gave dense precipitates with the solution. The substance, therefore, contained an alkaloid.

(d) The specific tests for the identification of the known volatile alkaloids, such as nicotine, in all cases gave negative results.

(e) Vitali's test gave a brilliant red colour, which indicated the presence of an alkaloid of the atropine group.

(f) The solution was diluted to 1 part of residue in 500 normal saline (1 in 1000 alkaloid), and when one drop of this was instilled into the eye of a dog, wide dilatation was produced in about 20 minutes. The alkaloid was therefore of the midriatic group.

Evidence was thus obtained from these results that the alkaloids assumed to be non-volatile, had distilled over in small quantities, under the conditions stated. The next step, therefore, was to ascertain the behaviour of pure atropine, when treated in the same way.

xvi. *Control experiment.*—*Method*:—Pure atropine sulphate solutions with excess of lime, with and without sawdust, were distilled in a current of steam, from a flask fitted with a Kjeldahl spray-trap. At the end of each hour, the distillate which reacted alkaline to litmus, was shaken out with chloroform. The chloroform extract was then washed and dried, and the solvent distilled off. The residues were weighed and titrated, and afterwards examined.

Results:—Very erratic results were obtained. In some, the amount of residue decreased to nothing in the five successive hours. In others, they varied much, even increasing at the end. In general, a total weight of 20 mgs. was obtained after five hours. This yield was apparently independent of the amount of alkaloid taken, which was between 0.1 and 1.0 mg. The addition of sawdust did not alter the result. All the residues contained alkaloid.

When a distillate, without previous neutralisation, was evaporated in an open basin over a bunsen flame, the residue contained only a trace of alkaloid.

(a) By titration of these residues as in the previous series, the amount of alkaloid (as atropine) in five hours' distillation was 11 mgs. If the latter be taken as representing the actual amount of alkaloid in each total distillate, then the alkaloid has distilled over under the conditions of these experiments at a rate of 2 mgs. per hour. From these titrated solutions, the alkaloid was recovered and examined.

(b) The aqueous solution, faintly acidulated, possessed a very bitter taste, and alkaline reaction to litmus.

(c) Dense precipitates were obtained with all the general alkaloid reagents.

(e) On applying Vitali's test for atropine, a deep red colour was shown.

(f) The solution was brought to 1 in 1000 with normal saline, and one drop of this instilled into the eye of a dog. Almost complete dilatation was produced within 30 minutes.

The distillate therefore contained atropine, and the results showed that when solutions of atropine are distilled in a current of steam, the alkaloid volatilises. Also, when very dilute solutions of atropine are evaporated by boiling in an open basin, the alkaloid may be almost entirely lost.

APPLICATION OF THE RESULTS.

xvii. *The Statement.*—The foregoing experiments afford conclusive evidence that, when leaves of *Duboisia myoporoides* were distilled with alkali in a current of steam, an alkaloid volatilised and was obtained in the distillate. This alkaloid was a minute proportion of the atropine and hyoscyamine, which are known to be present in the leaves, and which have always been assumed to be non-volatile.

When solutions of pure atropine were distilled in the same apparatus, and under the same conditions, atropine distilled over, and almost at the same rate as from the plant, 1-2 mgs. per hour.

The Interpretation.—We are now enabled by these results to interpret some of the contradictory statements of the earlier investigators. *D. Hopwoodii*, the first to be examined chemically, had yielded nicotine, and from the closely related *D. myoporoides* an alkaloid was obtained in the same way as nicotine. In the extraction of the midriatic alkaloids, even with modern improvements, the crude product first obtained is invariably a viscous, oily liquid, or syrupy residue. One must not, however, assume that it contains any of the liquid alkaloids, such as nicotine, since the residue will eventually crystallise when properly puri-

fied. Even pure atropine, when dissolved in chloroform, alcohol, or water, and the solution evaporated on the water-bath, is left as a syrupy residue. If these viscous semi-fluid residues be distilled, as described, the distillates will yield all the tests for the alkaloid, and so the isolation of the "volatile, liquid alkaloids, piturine and duboisine," is explained.

The early experimenters were thrown off the track again, in their attempt to solve this difficult problem, by another factor—the "strong odour of tobacco." This is stated frequently in the literature, and no doubt played a large part in setting the bias towards nicotine. During the chemical investigation of many other solanaceous plants, especially *Solandra*, the *Solanums*, and *Nicotiana* species, the author has noted the strong odour which makes itself prominent at certain stages. It is particularly strong when a solution is evaporated to dryness, and when the chloroform is distilled off from the last extract; and a syrupy residue is left, which contains the crude alkaloids. This residue, in all the cases just mentioned, possessed this peculiar odour—powerful, nauseous, and disagreeable. It somewhat resembles very stale nicotine or conine, but is due to a volatile essential oil which is probably present in all these plants. It was isolated from the steam-distillates previously described, by acidulating and shaking out with ether. When the ether was slowly removed at air-temperature, the residue exhibited all the objectional properties described. This residue gave no alkaloidal reactions.

It is thus shown that the statements "a volatile, liquid alkaloid possessing the odour of tobacco," and "consisting of atropine or hyoscyamine," are both correct, and in accordance with experimental facts.

" DUBOISINE."

xviii. The chemical history of the midriatic alkaloids, which have been isolated from *Duboisia myoporoides*, possesses peculiar interest and importance. "Duboisine," the commercial crude drug, is still extracted, and is found in commerce as the total mixed alkaloids. In 1912, Merck's pure crystallised duboisine

How are these variations to be explained? Ladenburg has stated that they were due to different methods of manufacture, but he believed that his hyoscyine was a true isomer of hyoscyamine, and therefore his opinion was legitimate. We are now certain that these two bases possess a different chemical composition, and therefore cannot be transformed in this way, so that Schmidt's view was nearer the truth—that the leaves sometimes contained hyoscyamine, and at other times scopolamine. Our present biochemical knowledge, however, will scarcely admit of this view, that a plant under variable conditions may alter its fundamental chemical products. But it is quite possible that variations in the conditions of growth influence the relative amount of each of these bases, by stimulating and causing a predominance of one, or by reducing the production of another to a minimum amount. The plants probably contain all the alkaloids in question, and none is entirely absent at any time. The detection of the small amounts of one of these alkaloids in the mixture requires the greatest skill and patience, and in most of the papers cited the authors omit the details of manipulation by which alone the value of their results can be estimated.

This example of the variation of the tropeines in the *Duboisia* is analogous to that of the cocaine in *Erythroxylon*, and to the strychnine and brucine in the *Strychnos* plants.

CHEMICAL COMPOSITION COMPARED.

xix. The two *Duboisias*, whose history we have been tracing, are thus shown to contain the widely different active principles, nicotine and hyoscyamine, while the original botanical descriptions of the two plants have much in common.

In order to bring out any further points of interest in the comparison of these two plants, a complete chemical analysis of the proximate constituents was made.

In each case, the air-dried leaves were submitted to successive extractions with organic solvents, and the extracts further analysed. The results of these analyses are given in the accompanying table.

The *Duboisia Hopwoodii* was part of a stock in the possession of Sir Thomas Anderson Stuart, to whose kindness the author is much indebted. After its long journey from the interior, the pituri plant is received in the form of very dry leaf-fragments mixed with broken stalks and twigs. The leaf-portion, constituting 50% of the whole, was carefully separated from the sample, and finely powdered for the analysis.

The *Duboisia myoporoides* was collected in the National Park by the kind permission of the Trustees. The leaves were taken from trees about 25 feet high and at the time of flowering.

The *Duboisia Leichhardtii* F.v.M., is a third species, whose chemical composition is yet unknown. It was collected by the author, near the Stuart River in Queensland, at the same time of year as in the preceding specimen, and while in flower.

The total alkaloids in each plant were also estimated, and the results are given in the accompanying table.

The author desires to express his thanks to Sir Thomas Anderson Stuart for laboratory facilities afforded during this investigation.

AMOUNT OF TOTAL ALKALOIDS.

	Air-dried.	Dried at 100°, ash-free.	Fresh.
<i>Duboisia Hopwoodii</i> , leaves ..	1.00%	1.36%	0.27%
<i>D. Leichhardtii</i> , leaves ...	1.28	1.42	0.28
<i>D. myoporoides</i> , mature leaves ...	0.17	0.21	0.04
<i>D. myoporoides</i> , seedling leaves ...	0.073	0.082	0.017
<i>D. myoporoides</i> , bark	0.027	...

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